REMARKS

## *I. Status Summary*

Claims 1-36 as filed in the instant U.S. patent application were subject to a Restriction/Election Requirement. In response to the Restriction/Election Requirement, Applicant elected the claims of Group I, claims 1-17, for prosecution at this time.

Claims 18-36 have been withdrawn from consideration. Claims 1-17 are pending and have been examined by the U.S. Patent and Trademark Office (hereinafter, "Patent Office").

Claims 1-17 have been rejected under the provisions of 35 U.S.C. §112, first paragraph.

Claims 1 and 10 have been rejected under the provisions of 35 U.S.C. §112, second paragraph.

Claims 1, 3, 10 and 12 have been rejected under 35 U.S.C. §102(b) as being anticipated by the journal articles of *Brown et al.* (1998) or *Uehara et al.* (1998).

Claims 1-17 have been rejected under 35 U.S.C. §103(a) as being obvious over *Brown et al.* (1998) in view of journal article to *Vaughan* (1997).

Applicant requests cancellation of claims 18-36 without prejudice. Applicant hereby reserves the right to file one or more divisional patent applications to the subject matter of previously withdrawn and now cancelled claims 18-36. Additionally, Applicant requests addition of new Claims 37, 38, and 39.

Claim 1 has been amended to more particularly claim the present invention. Claim 5 has been cancelled and re-written as claim new 39 to correct improper dependency of the claim.

New claims 37 and 38 have been added. New claims 37 and 38 represent the subject matter of the elected invention. Support for new claims 37 and 38 can be found in the claims and specification as originally filed. Specifically, support for claim 37 can be found in claim 3 and page 9, line 22 through page 10, line 3 of the application and support for claim 38 can be found in claim 4 and page 10, lines 12-25. Therefore, no new matter is introduced by new claims 37 and 38.

Reconsideration of the application as amended and based on the arguments set forth herein below is respectfully requested.

## *II. Response To 35 U.S.C. §112, First Paragraph Rejections*

Claims 1-17 are rejected under 35 U.S.C. §112, first paragraph. The Patent Office states that the claims are rejected because "the specification, while being enabling for reducing risk of cardiovascular disease, does not reasonably provide enablement for prevention of such disorders." Official Action at pages 2-3; emphasis added.

Respectfully, Applicant neither agrees nor acquiesces to the analysis by the Patent Office. Applicant maintains that the disclosure of the specification as filed adequately enables the claims as filed, and conveys to one of skill in the art that the Applicant was in full possession of the claimed invention at the time of the filing of the application.

However, for the purpose of expediting prosecution of the present application, claim 1 has been amended to remove the term "preventing". Applicant respectfully notes that the term "preventing" is not found in claim 10 as originally filed, and

therefore the above-noted rejection as applied to claims 10-17 is believed to be improper.

In view of the foregoing, Applicant respectfully submits that the 35 U.S.C. §112, first paragraph rejection related to enablement issues have been rendered moot. Accordingly, withdrawal of this rejection is respectfully requested.

### *III. Response To 35 U.S.C. §112, Second Paragraph Rejections*

Claims 1 and 10 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Official Action at page 6. Particularly, the Patent Office contends that claims 1 and 10 are indefinite because the metes and bounds of the phrase "healthy subject" are not clearly delineated, in that the term "healthy" is vague and the boundaries of the term cannot be determined readily.

Applicant respectfully traverses this rejection. The term "healthy" has been given a clear definition in the specification. As defined at pages 9-10 of the specification, the term "healthy" refers to a state of being of the subject wherein the subject is "free of hypertension, congestive heart failure, left ventricular dysfunction, and prior myocardial infarct, or induced activation of the renin-angiotensin system." The term "healthy" also excludes certain conditions. In particular, a healthy subject is one not at high risk for cardiovascular diseases. In one example, a subject would not be considered healthy due to a risk of cardiovascular disease if they were aged 55 years or older and had evidence of vascular disease or diabetes. *See* pages 9-10 of Specification.

Summarily, Applicant respectfully submits that claims 1 and 10 are in compliance with 35 U.S.C. § 112, second paragraph, as the phrase "healthy subject" is clearly defined at pages 9-10 of the specification, among other places. Withdrawal of the rejection of claims 1 and 10 under 35 U.S.C. § 112, second paragraph, is therefore respectfully requested.

### *IV. Response To 35 U.S.C. §102(b) Rejection*

A. *Brown et al.* (1998)

Claims 1, 3, 10 and 12 have been rejected under 35 U.S.C. §102(b) as being anticipated by the journal article of *Brown et al.* (*Hypertension*, 1998; 32:965-971), hereinafter "*Brown et al.*" The Patent Office contends *Brown et al.* teaches that ACE inhibition of the RAS decreases progression of atherosclerosis in animal models and reduces the risk of recurrent MI in patients with left ventricular dysfunction. The Patent Office further contends the test subjects were free from cardiovascular diseases.

Applicant respectfully traverses the Patent Office on this rejection. "A claim is anticipated only if each and every element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The present claims recite methods for either significantly reducing a risk of cardiovascular disease or reducing a plasma level of PAI-1 in a healthy subject by administering an effective dose of an ACE inhibitor to the healthy subject, whereby the risk of cardiovascular disease or the plasma level of PAI-1 in the healthy subject is significantly reduced. As discussed above, the term "healthy" as defined in the

specification refers to a state of being of the subject wherein the subject is "free of hypertension, congestive heart failure, left ventricular dysfunction, and prior myocardial infarct, or induced activation of the renin-angiotensin system." The term "healthy" also excludes certain conditions. In particular, a healthy subject is one not at high risk for cardiovascular diseases, such as subjects aged 55 years or older and having evidence of vascular disease.

*Brown et al.* does not teach administering an ACE inhibitor to a healthy subject in order to significantly reduce a risk for cardiovascular disease in the healthy subject. Rather, *Brown et al.* studied the effect of salt depletion on tPA and PAI-1 activity in the presence or absence of quinapril. *Brown et al.* did not study reducing the risk of cardiovascular disease in healthy subjects, but instead in subjects having a simulated disease state (activation of renin-angiotensin system) by severely limiting the salt intake (10 mmol/day) of the test subjects. *See Brown et al.* at page 966. *Brown et al.* also teaches that ACE inhibition of the RAS decreases progression of atherosclerosis in animal models and reduces the risk of recurrent MI in patients with left ventricular dysfunction. Again, patients with progressive atherosclerosis, previous MI or ventricular dysfunction are not healthy subjects as clearly defined in the specification and set forth in the claims. Therefore, *Brown et al.* does not teach significantly reducing a risk of cardiovascular disease or plasma levels of PAI-1 in a healthy subject, as set forth in the claims.

Since *Brown et al.* does not teach each and every element of any of the claims, Applicant respectfully submits that maintaining a rejection under 35 U.S.C. § 102 of any of the pending claims based on the cited art is improper. Withdrawal of

the rejection of claims 1, 3, 10 and 12 under 35 U.S.C. § 102, is therefore respectfully requested.

B. *Uehara et al.*

Claims 1, 3, 10 and 12 have been rejected under 35 U.S.C. §102(b) as being anticipated by the journal article of *Uehara et al.* (*J Cardiovasc Pharmacol Therapeut*, 1998; 3(4):327-36), hereinafter "*Uehara et al.*" The Patent Office contends *Uehara et al.* studied ACE inhibition on PAI-1 in diabetic rats, and that PAI-1 concentrations in plasma were significantly increased in untreated OLETF rats (a genetically modified rat strain that develops diabetes) compared to control non-diabetic rats.

Applicant respectfully traverses the Patent Office on this rejection. "A claim is anticipated only if each and every element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The present claims recite methods for either significantly reducing a risk of cardiovascular disease or reducing a plasma level of PAI-1 in a healthy subject by administering an effective dose of an ACE inhibitor to the healthy subject, whereby the risk of cardiovascular disease or the plasma level of PAI-1 in the healthy subject is significantly reduced. As discussed above, the term "healthy" as defined in the specification refers to a state of being of the subject wherein the subject is "free of hypertension, congestive heart failure, left ventricular dysfunction, and prior myocardial infarct, or induced activation of the renin-angiotensin system." The term "healthy" also excludes certain conditions. In particular, a healthy subject is one not

at high risk for cardiovascular diseases, such as subjects aged 55 years or older and having evidence of vascular disease.

*Uehara et al.* does not teach administering an ACE inhibitor to a healthy subject in order to significantly reduce a risk for cardiovascular disease in the healthy subject. Rather, *Uehara et al.* studied the effect of ACE inhibitors on reduction of diabetes onset in rats with a genetic predilection for diabetes. The present claims encompass significantly reducing a risk for cardiovascular disease in healthy subjects. As defined in the specification, "healthy" specifically excludes subjects with diabetes. *See* specification at pages 9 and 10. Further, *Uehara et al.* studies a rat diabetes model, which is not applicable to cardiovascular disease. Therefore, *Uehara et al.* does not teach significantly reducing a risk of cardiovascular disease or plasma levels of PAI-1 in a healthy subject, as set forth in the claims.

Since *Uehara et al.* does not teach each and every element of any of the claims, Applicant respectfully submits that maintaining a rejection under 35 U.S.C. § 102 of any of the pending claims based on the cited art is improper. Withdrawal of the rejection of claims 1, 3, 10 and 12 under 35 U.S.C. § 102, is therefore respectfully requested.

### *V. Response To 35 U.S.C. §103(a) Rejection*

Claims 1-17 stand rejected by the Patent Office under 35 U.S.C. § 103(a) as being unpatentable over *Brown et al.* in view of *Vaughan* (*Am J Cardiol*, 1997; 79(5A):12-16), hereinafter "*Vaughan*". The Patent Office asserts that *Brown et al.* teaches all the elements of original claim 1 except wherein the ACE inhibitor is ramipril, wherein the ACE inhibitor is administered to a person having a PAI-1

polymorphism which resulted in elevated PAI-1 or wherein the method reduced PAI-1 by at least 35% compared to baseline. The Patent Office further asserts *Vaughan* teaches that increased blood PAI-1 levels are a key in thrombus development leading to cardiovascular complications and that it would have been obvious at the time of the invention for one of skill in the art to have altered the teachings of *Brown et al.* with those of *Vaughan* so as to provide a method inclusive of all the elements of the present claims.

The positions of the Examiner as summarized above with respect to claims 1-17 are respectfully traversed as described below.

Applicant respectfully submits that neither *Brown et al.* nor *Vaughan*, either alone or in combination, teach or suggest all the elements of either of claims 1 or 10. As previously stated, *Brown et al.* does not teach or suggest administering an ACE inhibitor to a healthy subject in order to either significantly reduce a risk for cardiovascular disease or reduce plasma levels of PAI-1 in the healthy subject. *Vaughan* does not supplement this lack of teaching. *Vaughan* only suggests ACE inhibitor therapy as having benefit in patients with cardiovascular disease, such as post-MI, hypertensive and left ventricular function patients. *See Vaughan*, pages 13, 14 and 15, respectively. *Vaughan* does not teach or suggest ACE inhibitor therapy in healthy subjects.

Since all the features of either of claims 1 or 10 are neither taught nor suggested by *Brown et al.* and *Vaughan*, either alone or in combination, it is respectfully submitted that claims 1 and 10 are now in proper condition for allowance. Applicant therefore respectfully requests withdrawal of the rejection of claims 1 and

10 based on *Brown et al.* in view of *Vaughan*. As claims 2-9 and claims 11-17 depend either directly or indirectly from claims 1 and 10, respectively, and *Brown et al.* and *Vaughan*, do not teach or suggest, either alone or in combination, all the elements of claims 1 and 10 for the reasons stated above, *Brown et al.* and *Vaughan* therefore do not teach or suggest all the elements of these dependent claims either. Applicant therefore respectfully requests withdrawal of the rejection of claims 2-9 and 11-17 on the basis of *Brown et al.* in view of *Vaughan*.

### *VI. New Claims 37 and 38*

Claim 37 recites a method for significantly reducing a risk of cardiovascular disease in a subject free of hypertension, congestive heart failure, left ventricular dysfunction, prior myocardial infarct, and induced activation of the renin-angiotensin system by administering an effective dose of an ACE inhibitor to the subject. None of the cited art teaches or suggests reducing a risk of cardiovascular disease in a subject free of hypertension, congestive heart failure, left ventricular dysfunction, prior myocardial infarct, and induced activation of the renin-angiotensin system. *Brown et al.* studies a simulated disease state by induced activation of the renin-angiotensin system in test subjects. *Uehara et al.* studies rats genetically modified to develop diabetes, which exhibit hypertension as a result of their diabetic state. *Vaughan* only proposes ACE inhibitor therapy as having benefit in patients with cardiovascular disease. Therefore, Applicant respectfully submits that none of the cited art teaches or suggests, either alone or in combination, each and every element of new claim 37.

Claim 38 provides a method for significantly reducing a risk of cardiovascular disease in a post-menopausal female human subject by administering an effective dose of an ACE inhibitor to the subject. None of the cited art teaches or suggests reducing a risk of cardiovascular disease in a post-menopausal female human subject. *Brown et al.* uses young male subjects stimulated to produce a state of induced activation of the renin-angiotensin system. *Uehara et al.* studies rats genetically modified to develop diabetes. *Vaughan* only proposes ACE inhibitor therapy as having benefit in patients with cardiovascular disease.

The Patent Office suggests the ordinary artisan would have been motivated to treat a post-menopausal woman with an ACE inhibitor in order to reduce a risk of cardiovascular disease because the woman might be expected to exhibit increased PAI-1 levels and these increased levels of PAI-1 have been associated with cardiology related diseases. However, not all studies available to the skilled artisan at the time of filing of the present application corroborated this suggestion. For example, a journal publication by Lottermoser et al. (*Eur J Med Res*, 1999; 4(1):31-35; Applicant IDS reference no. 22) describes a study of the effects of captopril, an ACE inhibitor, in healthy humans. In this study, administration of captopril for two weeks showed no significant effect on PAI-1 levels. This study illustrates the ambiguity of the prophylactic effectiveness of ACE inhibitor administration for reduced risk of cardiovascular disease, particularly in post-menopausal female subjects. Thus, based on the teachings of *Lottermoser et al.*, a skilled artisan in the field would infer that ACE inhibition has no effect in reducing PAI-1 levels in healthy subjects.

Based on the conflicting reports in the literature prior to the present invention, Applicant respectfully submits that a skilled artisan would not be motivated to treat post-menopausal women with ACE inhibitors in order to reduce the risk of cardiovascular disease due to the overall ambiguity in the field as to the efficacy of such a practice. Therefore, Applicant respectfully submits that none of the cited art teaches or suggests, either alone or in combination, each and every element of new claim 38.

## CONCLUSIONS

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Application No. 09/974,703

**DEPOSIT ACCOUNT**

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 03/29/2004 By: _____
Arles A. Taylor, Jr.
Registration No. 39,395

1242/39/2 AAT/JD/cht

Customer No.: 25297